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Year: 2014

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## Does colonization with methicillin-susceptible *Staphylococcus aureus* protect against nosocomial acquisition of methicillin-resistant *S. aureus*?

Landelle, Caroline ; Iten, Anne ; Uçkay, Ilker ; Sax, Hugo ; Camus, Véronique ; Cohen, Gilles ; Renzi, Gesuele ; Schrenzel, Jacques ; Pittet, Didier ; Perrier, Arnaud ; Harbarth, Stephan

**Abstract:** **OBJECTIVE:** To test the hypothesis that methicillin-susceptible *Staphylococcus aureus* (MSSA) carriage may protect against nosocomial methicillin-resistant *S. aureus* (MRSA) acquisition by competing for colonization of the anterior nares. **DESIGN:** Prospective cohort and nested case-control study. **SETTING:** Swiss university hospital. **PATIENTS:** All adult patients admitted to 14 wards of the general medicine division between April 1 and October 31, 2007. **METHODS:** Patients were screened for MRSA and MSSA carriage at admission to and discharge from the division. Associations between nosocomial MRSA acquisition and MSSA colonization at admission and other confounders were analyzed by univariable and multivariable analysis. **RESULTS:** Of 898 patients included, 183 (20%) were treated with antibiotics. Nosocomial MRSA acquisition occurred in 70 (8%) of the patients (case patients); 828 (92%) of the patients (control subjects) were free of MRSA colonization at discharge. MSSA carriage at admission was 20% and 21% for case patients and control subjects, respectively. After adjustment by multivariate logistic regression, no association was observed between MSSA colonization at admission and nosocomial MRSA acquisition (adjusted odds ratio [aOR], 1.2 [95% confidence interval (CI), 0.6-2.3]). By contrast, 4 independent predictors of nosocomial MRSA acquisition were identified: older age (aOR per 1-year increment, 1.05 [95% CI, 1.02-1.08]); increased length of stay (aOR per 1-day increment, 1.05 [95% CI, 1.02-1.09]); increased nursing workload index (aOR per 1-point increment, 1.02 [95% CI, 1.01-1.04]); and previous treatment with macrolides (aOR, 5.6 [95% CI, 1.8-17.7]). **CONCLUSIONS:** Endogenous MSSA colonization does not appear to protect against nosocomial MRSA acquisition in a population of medical patients without frequent antibiotic exposure.

DOI: <https://doi.org/10.1086/675825>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-102411>

Journal Article

Published Version

Originally published at:

Landelle, Caroline; Iten, Anne; Uçkay, Ilker; Sax, Hugo; Camus, Véronique; Cohen, Gilles; Renzi, Gesuele; Schrenzel, Jacques; Pittet, Didier; Perrier, Arnaud; Harbarth, Stephan (2014). Does colonization with methicillin-susceptible *Staphylococcus aureus* protect against nosocomial acquisition of methicillin-resistant *S. aureus*? *Infection Control and Hospital Epidemiology*, 35(5):527-533.

DOI: <https://doi.org/10.1086/675825>



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Source: *Infection Control and Hospital Epidemiology*, Vol. 35, No. 5 (May 2014), pp. 527-533

Published by: [The University of Chicago Press](#) on behalf of [The Society for Healthcare Epidemiology of America](#)

Stable URL: <http://www.jstor.org/stable/10.1086/675825>

Accessed: 16/12/2014 10:59

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## ORIGINAL ARTICLE

# Does Colonization with Methicillin-Susceptible *Staphylococcus aureus* Protect against Nosocomial Acquisition of Methicillin-Resistant *S. aureus*?

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**OBJECTIVE.** To test the hypothesis that methicillin-susceptible *Staphylococcus aureus* (MSSA) carriage may protect against nosocomial methicillin-resistant *S. aureus* (MRSA) acquisition by competing for colonization of the anterior nares.

**DESIGN.** Prospective cohort and nested case-control study.

**SETTING.** Swiss university hospital.

**PATIENTS.** All adult patients admitted to 14 wards of the general medicine division between April 1 and October 31, 2007.

**METHODS.** Patients were screened for MRSA and MSSA carriage at admission to and discharge from the division. Associations between nosocomial MRSA acquisition and MSSA colonization at admission and other confounders were analyzed by univariable and multivariable analysis.

**RESULTS.** Of 898 patients included, 183 (20%) were treated with antibiotics. Nosocomial MRSA acquisition occurred in 70 (8%) of the patients (case patients); 828 (92%) of the patients (control subjects) were free of MRSA colonization at discharge. MSSA carriage at admission was 20% and 21% for case patients and control subjects, respectively. After adjustment by multivariate logistic regression, no association was observed between MSSA colonization at admission and nosocomial MRSA acquisition (adjusted odds ratio [aOR], 1.2 [95% confidence interval (CI), 0.6–2.3]). By contrast, 4 independent predictors of nosocomial MRSA acquisition were identified: older age (aOR per 1-year increment, 1.05 [95% CI, 1.02–1.08]); increased length of stay (aOR per 1-day increment, 1.05 [95% CI, 1.02–1.09]); increased nursing workload index (aOR per 1-point increment, 1.02 [95% CI, 1.01–1.04]); and previous treatment with macrolides (aOR, 5.6 [95% CI, 1.8–17.7]).

**CONCLUSIONS.** Endogenous MSSA colonization does not appear to protect against nosocomial MRSA acquisition in a population of medical patients without frequent antibiotic exposure.

*Infect Control Hosp Epidemiol* 2014;35(5):527–533

Risk factors and colonization patterns differ between methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA). The prevalence of MSSA carriage at hospital admission varies between 15% and 25%, similar to carriage in the community.<sup>1–3</sup> The admission prevalence of MRSA carriage in settings with endemic MRSA can vary substantially and is reported to range from 3% to 15%.<sup>4–7</sup>

Patients who acquire MRSA incur significant risks of subsequent infection.<sup>8–10</sup> Importantly, MRSA carriage is associated with a fourfold increased infection risk compared with

MSSA colonization.<sup>11,12</sup> Many studies have evaluated the risk factors for nosocomial MRSA acquisition (eg, comorbidities, exogenous factors, and antimicrobial exposure) to improve preventive measures,<sup>13–15</sup> but despite 50 years of research, less is known about the protective factors at the host level. It has been hypothesized that endogenous MSSA carriage may protect against exogenous MRSA acquisition by competing for colonization of the anterior nares.<sup>16</sup> In a retrospective case-control study, Huang and colleagues observed that MSSA carriage reduced the odds of MRSA acquisition by 50% in critically ill patients, after controlling for other risk factors.<sup>17</sup>

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Received October 11, 2013; accepted December 4, 2013; electronically published March 19, 2014.

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By contrast, a small retrospective study suggested that carriage of MSSA was not protective against MRSA acquisition.<sup>18</sup> Of note, both studies evaluated MRSA in the nares only.

The aim of this study was to test the hypothesis that endogenous MSSA colonization detected in the nares and groin may reduce the risk of exogenous, nosocomial MRSA acquisition. Our secondary objectives were to determine the MRSA acquisition rate and the prevalence of MSSA at admission and discharge.

## METHODS

### Study Setting

We conducted a prospective, nested case-control study at the University of Geneva Hospital, Geneva, Switzerland, in a cohort of patients admitted to 14 wards of the general internal medicine division between April 1 and October 31, 2007. The admission prevalence of MRSA among hospitalized patients in this department was 2.9% in 2003 and 2.4% in 2010.<sup>4,19</sup> Nares and groin samples were collected from patients at admission and discharge to detect MRSA and MSSA carriage. Hand hygiene was performed according to the World Health Organization "My 5 moments for hand hygiene" concept,<sup>20</sup> with a compliance of 66.3% (447 of 674) among healthcare workers during the study period. Contact precautions were applied to previously known MRSA carriers in case of re-admission and were implemented as soon as a newly discovered case of MRSA carriage was notified via an automatic laboratory alert system.<sup>21</sup> The institutional review board approved the study as a continuous quality improvement project for improved MRSA control; therefore, no informed consent was required.

### Study Design

We included patients older than 18 years of age who were hospitalized for more than 48 hours with a negative screening culture (nares and groin) for MRSA obtained at admission. Exclusion criteria were MRSA colonization or infection at admission, an interval less than 48 hours between admission and MRSA discharge screening, and lack of admission and/or discharge data on MRSA screening. Case patients were defined as subjects who had at least 1 subsequent MRSA-positive nares and groin screening culture at discharge or a MRSA-positive clinical culture; control subjects had all subsequent screening swab samples and clinical cultures without MRSA.

### Microbiologic Methods

Two nares and 2 groin *S. aureus* screening specimens from individual patients were pooled in the laboratory and inoculated directly onto SAURid and MRSAid plates (bio-Mérieux). Pooled swab samples were then inoculated into a colistin salt (CS) broth. When no MRSA was detected on chromogenic agar at day 1, a second SAURid plate and a

second MRSAid plate were inoculated after overnight enrichment in the CS broth. Identification of MSSA and MRSA from colonies suggestive of staphylococci were performed using standard methods<sup>4</sup> according to Clinical and Laboratory Standards Institute recommendations and confirmed with multiplex quantitative polymerase chain reaction (PCR) for the genes *femA* and *mecA*.<sup>22</sup>

### Data Collection

We collected demographic and clinical information prospectively. Additional data were obtained by retrospectively accessing electronic medical records. Nursing workload was evaluated by the Projet de Recherche en Nursing (PRN) index.<sup>23</sup> This index includes 8 categories of nursing procedures covering all technical, relational, and basic tasks. PRN items are scored routinely by the nurse in charge of each patient. The time-based work load for each patient is then calculated daily. Patient comorbidities were recorded according to the updated Charlson comorbidity index.<sup>24</sup> We also recorded antibiotic use by accessing individual inpatient prescription data, as previously described.<sup>25</sup>

### Statistical Analysis

Baseline characteristics were described by frequencies, medians, and interquartile ranges (IQRs). Groups were compared by means of the Mann-Whitney *U* test, Pearson  $\chi^2$  test, or Fisher exact test as appropriate for continuous and categorical variables. The main exposure of interest was MSSA colonization status at admission, and the primary outcome was nosocomial MRSA acquisition by patients initially free of MRSA. Variables potentially associated with nosocomial MRSA acquisition were tested using univariate analysis. Variables with a *P* value of less than or equal to .2 in univariable analysis were candidates for multivariable analysis, as was the main exposure of interest (MSSA colonization status at admission). Nonnormally distributed continuous variables were transformed into categorical variables on the basis of median values. Multivariable modeling was performed by using logistic regression analysis to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs). Interactions between the main exposure of interest and variables potentially associated with nosocomial MRSA acquisition were tested to assess effect modification. All statistical tests were 2-tailed, and a *P* value less than or equal to .05 was considered to be statistically significant. We used PASW, version 18 (SPSS), for all analyses.

## RESULTS

A total of 1,857 patients were admitted to the division during the study period. Nine hundred fifty-nine were excluded from additional analysis for the following reasons: 103 (5.5%) were known MRSA carriers at hospital admission, and 228 (12.3%) had a length of stay less than 48 hours. For 628 (33.8%) of the patients, screening was not performed either at admission

or discharge. Finally, 898 (48.4%) of the patients were included in the analysis (Figure 1).

Comparison between the 628 patients with missing screening data and the 898 patients with complete admission and discharge screening showed no difference for sex, length of stay (LOS), and previous antibiotic use. Patients with missed screening were younger, had a lower nursing workload index, and were more likely to have a malignancy than patients with complete screening.

Among the 898 patients who met the study inclusion criteria, 526 (58.6%) were men; median LOS was 8 days. One hundred ninety-two (21.4%) were MSSA carriers at admission, and 183 (20.4%) were treated with antibiotics (Table 1). Seventy (7.8%) of the patients (case patients) acquired nosocomial MRSA, including 3 symptomatic infections. Eight hundred twenty-eight (92.2%) of the patients (control subjects) were discharged from the division free of MRSA colonization (Figure 1). Characteristics of case patients and control subjects are shown in Table 1.

The effect of MSSA carriage at admission on the risk of nosocomial MRSA acquisition was first examined by univariate analysis and showed that the rates were almost identical in both groups: 14 nosocomial MRSA acquisitions (7.3%) were recorded among 192 MSSA carriers, compared with 56 nosocomial MRSA acquisitions (7.9%) among 706 MSSA-negative patients at admission (crude OR, 0.91 [95% CI, 0.50–1.68]). By contrast, 6 variables were found to be associated with an increased risk of nosocomial MRSA ac-

quisition by univariate analysis ( $P < .01$ ): age, LOS, number of comorbidities, nursing workload, ward allocation, and macrolide use (Table 1). No difference was observed for MSSA carriage between case patients and control subjects at discharge.

By multivariate regression analysis, 4 independent predictors of nosocomial MRSA acquisition were identified: older age (aOR per 1-year increment, 1.05 [95% CI, 1.02–1.08]), increased LOS (aOR per 1-day increment, 1.05 [95% CI, 1.02–1.09]), increased nursing workload index (aOR per 1-point increment, 1.02 [95% CI, 1.01–1.04]), and previous treatment with macrolides (aOR, 5.6 [95% CI, 1.77–17.73]). After adjustment for the above-mentioned independent risk factors, no association was observed between MSSA colonization at admission and nosocomial MRSA acquisition (aOR, 1.17 [95% CI, 0.60–2.30]). Age, sex, and the Charlson comorbidity index had no effect modification on the MSSA colonization status at admission.

Among 192 MSSA carriers identified at admission, 85 (44.3%) of the patients were still MSSA positive at discharge from the division, and 107 (55.7%) were MSSA negative after hospital stay (Figure 1). Among 706 patients without MSSA carriage at admission, 28 (4%) of the patients were MSSA positive after hospital stay. Of the 70 case patients with nosocomial MRSA acquisition, 14 were MSSA positive at admission. At discharge from the division, 8 became MSSA negative; none of the 56 MSSA-free patients at admission became MSSA positive.

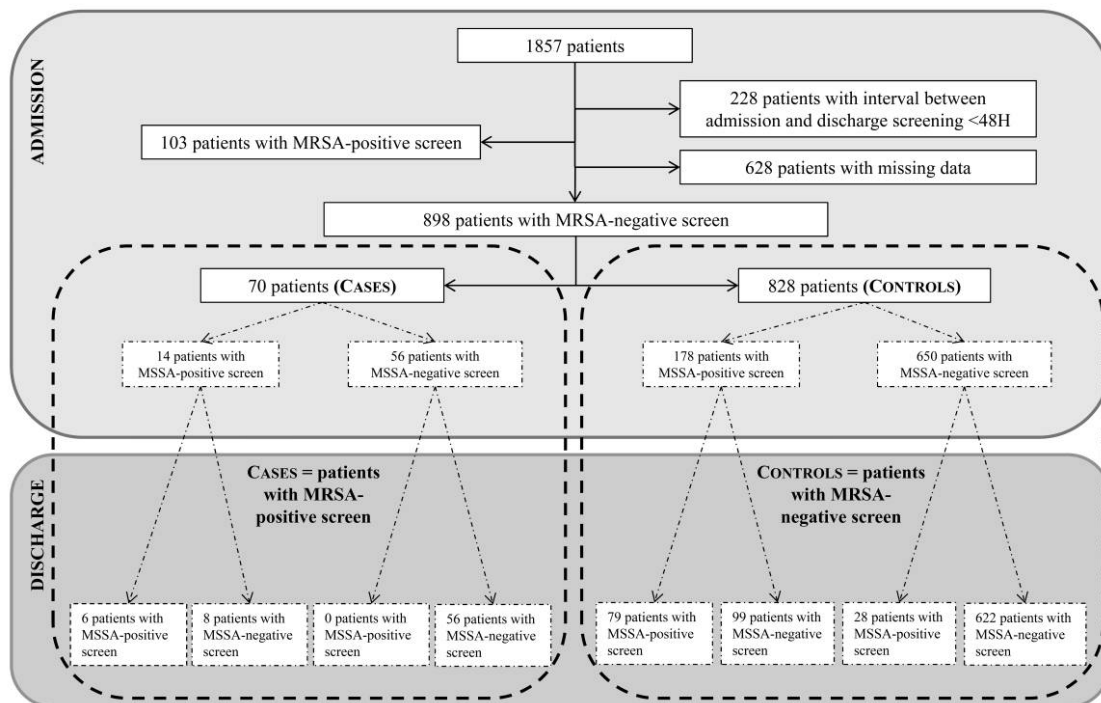


FIGURE 1. Study flow chart of patient inclusion and results of patient screening. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.



TABLE 1. Characteristics of Case Patients with and Control Subjects without Nosocomial Methicillin-Resistant *Staphylococcus aureus* (MRSA) Acquisition by Univariable Analysis

Variable	Total ( <i>n</i> = 898)	Case patients ( <i>n</i> = 70)	Control subjects ( <i>n</i> = 828)	<i>P</i>
Age, median (IQR), years	68.8 (56.0–79.3)	77.1 (69.1–83.5)	67.9 (55.1–78.8)	<.0001
Male sex	526 (58.6)	37 (52.9)	489 (59.1)	.31
Length of stay, median (IQR), days	8 (4–13)	12 (8.75–17.0)	8 (4–13)	<.0001
Mean daily nursing workload index, median (IQR)	33.3 (25.5–44.2) <sup>a</sup>	37.4 (29.0–51.7) <sup>b</sup>	32.8 (25.2–43.5) <sup>c</sup>	.003
MSSA carriage at admission	192 (21.4)	14 (20.0)	178 (21.5)	.77
MSSA carriage at discharge	113 (12.6)	6 (8.6)	107 (12.9)	.29
Comorbidities				
Congestive heart failure	127 (14.1)	15 (21.4)	112 (13.5)	.07
Dementia	20 (2.2)	2 (2.9)	18 (2.2)	.66
Chronic pulmonary disease	118 (13.1)	16 (22.9)	102 (12.3)	.01
Rheumatic disease	18 (2.0)	1 (1.4)	17 (2.1)	1.0
Mild liver disease	2 (0.2)	0	2 (0.2)	1.0
Diabetes with chronic complication	42 (4.7)	1 (1.4)	41 (5.0)	.24
Renal disease	74 (8.2)	10 (14.3)	64 (7.7)	.055
Any malignancy <sup>d</sup>	168 (18.7)	10 (14.3)	158 (19.1)	.32
Moderate or severe liver disease	17 (1.9)	0	17 (2.1)	.64
Metastatic solid tumor	73 (8.1)	4 (5.7)	69 (8.3)	.44
AIDS/HIV	6 (0.7)	1 (1.4)	5 (0.6)	.39
Charlson comorbidity index, median (IQR)	4 (3–6)	5 (4–7)	4 (3–6)	.005
Antibiotic use <sup>e</sup>	183 (20.4)	17 (24.3)	166 (20.0)	.40
Penicillin	63 (7.0)	5 (7.1)	58 (7.0)	1.0
Aminoglycoside	7 (0.8)	0	7 (0.8)	1.0
Macrolide	22 (2.4)	7 (10.0)	15 (1.8)	.001
Cephalosporin	37 (4.1)	3 (4.3)	34 (4.1)	.76
Fluoroquinolone	44 (4.9)	6 (8.6)	38 (4.6)	.14
Clindamycin	2 (0.2)	0	2 (0.2)	1.0
Anti-tuberculosis treatment	3 (0.3)	0	3 (0.4)	1.0
Carbapenem	13 (1.4)	2 (2.9)	11 (1.3)	.27
Metronidazole	6 (0.7)	1 (1.4)	5 (0.6)	.39
Anti-MRSA antibiotics <sup>f</sup>	22 (2.4)	2 (2.9)	20 (2.4)	.69

NOTE. Data are no. (%) of patients, unless otherwise indicated. Boldface type indicates statistical significance. AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IQR, interquartile range; MSSA, methicillin-susceptible *S. aureus*.

<sup>a</sup> *n* = 762.

<sup>b</sup> *n* = 62.

<sup>c</sup> *n* = 700.

<sup>d</sup> Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin.

<sup>e</sup> Assessed during stay and defined as the administration of antibiotics at least 1 day before the final negative or positive surveillance or clinical culture for MRSA.

<sup>f</sup> Anti-MRSA antibiotics include doxycycline, co-trimoxazole, rifampin, vancomycin, and teicoplanin.

## DISCUSSION

Our results do not confirm the hypothesis that MSSA colonization protects against nosocomial MRSA acquisition in a population of medical patients without strong antibiotic selection pressure. By contrast, our findings confirm well-known risk factors for nosocomial MRSA acquisition such as age, LOS, nursing workload, and previous treatment with macrolides.

There is historical evidence that colonization with a specific *S. aureus* strain prevents exogenous colonization with other strains. Bacterial interference by active colonization using a

nonpathogenic *S. aureus* strain (502A) was successful in child nurseries during staphylococcal outbreaks in the 1960s and for the treatment of patients with recurrent furunculosis.<sup>26,27</sup>

More recently, Dall'Antonia et al<sup>16</sup> tested the hypothesis that MRSA strains compete with MSSA for colonization of the anterior nares. Using a cross-sectional approach in 3 UK hospitals, the authors found a lower prevalence of co-carriers than expected and estimated a protective effect of MSSA colonization of 78% for the prevention of MRSA carriage.

The association between endogenous MSSA carriage and its potential protective effect against nosocomial MRSA ac-

quisition has not been extensively studied. The few published studies have shown contradictory results.<sup>17,18</sup> For instance, Krebes et al<sup>18</sup> showed that noncarriers of MSSA were not more susceptible to acquiring MRSA compared with MSSA carriers. Among 840 included patients, 9 (21.4%) of 42 patients who acquired MRSA during their hospitalization versus 178 (23%) of 775 patients who did not acquire MRSA were MSSA carriers. These results and our findings stand in contrast to a recent US study that suggests that MSSA carriage may reduce the odds of MRSA acquisition by 50% in intensive care units.<sup>17</sup> This discrepancy may be explained by differences in case mix, patient host factors, intensity of contact with healthcare personnel, and frequency and type of antibiotic exposure.

Consistent with earlier reports on MRSA acquisition, we found that patients who acquired nosocomial MRSA were older,<sup>28</sup> had longer LOS,<sup>15,17,29,30</sup> and more frequent exposure to macrolides.<sup>31</sup> Interestingly, we found no statistical association with fluoroquinolones and cephalosporins,<sup>13,14,17,32</sup> but this is possibly related to a lack of power due to the low number of patients exposed to these antibiotics in our population. We also observed that higher nursing workload was a risk factor of nosocomial MRSA acquisition. Several studies have linked overcrowding, understaffing, or nursing workload with cross-transmission of MRSA, *Enterobacteriaceae*, or gastrointestinal viruses.<sup>33,34</sup>

Regarding MSSA, we observed that 56% of MSSA carriers at admission became MSSA negative after hospital stay. The observed disappearance of MSSA at discharge from the division may be explained by (1) possible intermittent MSSA carriage;<sup>2,35</sup> (2) the previous exposure to antibiotics,<sup>35</sup> because most commonly used antibiotics have activity against MSSA; and (3) the effect of other in-hospital interventions not assessed in our study (eg, body cleaning with antiseptic soaps). A total of 4% of patients free of MSSA carriage at admission became MSSA positive, and 8% of patients free of MRSA carriage at admission became MRSA positive. We cannot attribute the 4% of MSSA positivity at discharge to a nosocomial acquisition. Transient MSSA carriage has been well described in the medical literature,<sup>2,35</sup> but this is not the case for healthcare-associated MRSA carriage among patients. Moreover, in our community, we have very limited community-associated MRSA carriage; incidence was 4 cases per 100,000 inhabitants in 2007.<sup>36</sup> These factors decrease the likelihood of intermittent MRSA carriage compared with the phenomenon frequently observed for MSSA.

Among the 70 cases with nosocomial MRSA acquisition, none of the 56 MSSA-free patients at admission became MSSA positive. We did not record simultaneous, nosocomial co-acquisition of both MRSA and MSSA. This could be explained by currently used microbiology methods, which make it difficult to detect low-level carriage of MSSA in the presence of heavy MRSA colonization.<sup>37</sup> Furthermore, there may be competition between MSSA and MRSA during hospital stay among patients initially free of any *S. aureus* carriage. For

instance, Dall'Antonia et al<sup>16</sup> found 4 patients (0.6%) among 680 who carried both MRSA and MSSA. Nosocomial acquisition of both MSSA and MRSA is possible but seems to be a very rare event.

Our study has limitations. First, a relatively high proportion of patients was missed at admission or discharge screening, as previously reported.<sup>19</sup> Nevertheless, the included patient population was diverse and is probably representative of the population encountered in other medical units. Furthermore, it is unlikely that a higher recruitment would have substantially modified the main effect estimate. Second, we were not able to adjust our model for colonization pressure. However, in a recent review by Ajao et al<sup>38</sup> that included 8 studies of risk factors for MRSA acquisition, only 3 found colonization pressure to be significantly associated with acquisition. Third, we cannot exclude that admission screening could have been insufficiently sensitive as a result of a low bacterial burden at sampled sites or incorrect sampling. However, we are confident that we have captured the majority of carriage by screening an additional body site (groin) in contrast to most previous studies cited above. Groin swab was chosen to detect patients with gastrointestinal MRSA carriage<sup>39</sup> and to increase the yield of nasal screening only.<sup>40</sup> We have previously determined at our institution that the addition of throat screening did not significantly improve the accuracy of detecting MRSA colonization.<sup>41</sup> Fourth, swabs were pooled before inoculation to decrease the cost of analyses. Therefore, acquisition rates by body site could not be calculated. Finally, this study was conducted among internal medicine patients at a single institution, and our findings might not be generalizable to other settings.

In conclusion, our study presents a new perspective on the interaction between endogenous MSSA colonization and nosocomial MRSA acquisition and provides a strong quantitative basis on this subject. Additional research is necessary to investigate whether MSSA colonization in patient populations with a different case-mix and antibiotic exposure patterns may have a different protective effect.

## ACKNOWLEDGMENTS

We thank F. Maitre, J. Maurin, C. Fankhauser, and J. Iavindrasana for their help with this study and R. Sudan for her substantial editing contribution.

*Potential conflicts of interest.* J.S. reports being a medical advisor to bioMérieux. S.H. reports having received a peer-reviewed research grant funded by Pfizer; he is also a member of the speakers' bureau for bioMérieux and a member of the advisory board of Destiny Pharma, bioMérieux, and DaVolterra. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Presented in part: 53rd Interscience Conference on Antimicrobial Agents

and Chemotherapy; Denver, Colorado; September 10–13, 2013 (Presentation K-1536).

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